Scientists offer way to address 'age-old' questions

September 7 2011

Scientists have devised a method to measure the impact of age on the growth rates of cellular populations, a development that offers new ways to understand and model the growth of bacteria, and could provide new insights into how genetic factors affect their life cycle. The research, which appears in *Evolution: International Journal of Organic Evolution*, was conducted by scientists at New York University and the University of Tokyo.

When bacterial cells age, their capacity for reproduction is reduced. Individual cells within populations are subject to the force of selection, which results from differences in growth rates. Broadly speaking, growing populations are dominated by relatively young cells. A population's age structure, however, depends sensitively on the interplay between selection and the reproductive capacities of the cells.

The researchers sought to understand how changes in cells' reproductive capacity would affect the population's growth rate. This question dates back to seminal research in population genetics by Ronald Fisher in the 1930s and William Hamilton in the 1960s. Typically, the answer is indirect, and relies on a measured life table and reproductive capacity, which takes into account survival and birth rates.

The NYU and University of Tokyo researchers hypothesized that a more direct gauge would be to examine the bacteria's lineages—their history over several generations. In other words, they proposed looking backward several generations into the population's tree of cell divisions.

This allowed them to directly measure the response of the bacteria's growth rate to age-specific changes in mortality and reproductive capacity.

"The force of selection within populations leaves key signatures in the population's lineage tree," said Edo Kussell, a professor of biology at NYU's Center for Genomics and Systems Biology and the study's corresponding author. "Theory allows us to interpret these in powerful ways. For instance, we found that how frequently a given age is observed along lineages is a direct reporter of how important that age is to the population's growth rate. This would allow us to predict the success or failure of mutant bacteria, which age differently from normal ones."

Using experimental data from laboratory populations of E. coli, the researchers confirmed several theoretical predictions. The article's other co-authors were Yuichi Wakamoto of the University of Tokyo and the Japan Science and Technology Agency and Alexander Grosberg, a professor in NYU's Department of Physics and its Center for Soft Matter Research.

The work builds upon a previously published paper in the Proceedings of the National Academy of Sciences, in which Kussell and co-author Stanislas Leibler of Rockefeller University offered a way to infer the behavior of individual cells from population-level measurements.

One of the behaviors they considered is known as stochastic switching, a strategy in which cells randomly activate certain genes in order to survive. Notably, pathogenic bacteria, which cause disease in both humans and animals, engage in stochastic switching, resulting in alternative cellular states that improve the bacteria's ability to survive. The cells best suited for given conditions survive while others die off—another example of selection within populations. Understanding what prompts this type of cellular change in bacteria, and which strains

are more sustainable than others, could then lead to alternative methods to curb bacterial growth.

The study centered on understanding two types of cellular strategies—responsive switching, in which cells change their state by reacting to environmental change, and stochastic switching, in which cells randomly activate certain genes, independent of external forces. Within a population, however, it is difficult to detect which strategy is being used—when cells change behavior, are they responding to their environment or is the change random?

Kussell and Leibler sought to develop a method that could disentangle these strategies. They showed that individual histories of cells—their lineages—would reveal differences between stochastic and responsive switching.

"Since stochastic switching organisms rely on selection to survive, we expected that if we could measure the strength of selection, we could distinguish the two strategies," Kussell said. "Once again, selection leaves a key signature in the population's lineage tree. In this case, the signature is the variance in cell divisions between lineages. If we measure that, then we can tell which strategy the cells are using internally."

The researchers simulated bacteria growing under fluctuating environmental conditions, and applied their lineage-based tests. This allowed them to show that the lineage tree indeed contains sufficient information to distinguish the two cellular strategies.

The importance of stochastic switching has recently been demonstrated in populations of cancer cells. With improved lineage tracking tools for cancer cells, it may soon become possible to apply some of the ideas that Kussell and co-workers have been developing in the bacterial context,

also in other systems, such as tumor and stem cell populations.

Provided by New York University